polymeric blocks comprising proteins or peptides which include imidazole groups.--

--30. The composition of claim 1 wherein the second polymeric or monomeric unit is a lipid or phospholipid.--

--31. The composition of claim 1 wherein the second polymeric or monomeric units comprise sulfonated groups.--

--32. The composition of claim 1 wherein the second polymeric or monomeric unit is sensitive to a stimulus selected from the group consisting of temperature, light, electrical stimuli, radiation, and ion concentration.--

**Remarks**

Claims 1-20 are pending. Claim 1 has been amended to clarify the claimed invention by specifying that the composition enhances transport of agent through lipid-containing membranes and that the composition includes a pH-sensitive polymer conjugated to a second polymeric or monomeric unit. Support for the amendment is found, for example, at page 6, lines 9-18; page 10, lines 6-12 and 21-24; page 10, line 31 to page 14, line 2; page 13, lines 8-11 and 24-31; page 14, lines 12-13 and 29-30; page 15, lines 8-10; page 16, line 24 to page 17, line 2; page 17, lines 12-27; and page 18, lines 6-12.

Claims 5, 7, 8, 11, and 15 have been amended to clarify the claimed compositions and methods in light of the amendment to claim 1. Claims 12 and 13 were amended to clarify the Markush groups. Claim 13 also was amended to include micelles. Support for the amendment is found, for example, at page 11, lines 17-23 and page 17, lines 17-19. Claim 20 has been

amended to correct a spelling error. Claims 2-4, 6, 14, and 16 have been canceled.

New claims 21-32 have been added. Support for new claims 21-25 is found, for example, in claims 1-4, 14, and 16 as originally filed. Support for new claim 26 is found at least at page 11, lines 27-30; and page 24, lines 25-31. Support for new claim 27 is found in claim 13 as originally filed and at page 11, lines 17-23 and page 17, lines 17-19. Support for new claims 28-29 is found at least at claim 7 as originally filed. Support for new claim 30 is found at least at page 14, lines 23-30. Support for new claim 31 is found at least at page 11, lines 9-26. Support for new claim 32 is found at least at page 17, line 4 to page19, line 15. A copy of the claims as currently pending is provided in the attached Appendix for the convenience of the Examiner.

**I. Applicants' Claimed Compositions and Methods**

Applicants have developed compositions and methods for improved transport across lipid-containing membranes, such as those of the exterior of cells, for the enhance delivery of therapeutic and diagnostic agents, across, for example, cell membranes, such as those of endosomal vesicles within cells. The compositions include (1) a pH-sensitive polymer which does not disrupt cell membranes at physiological pH but which disrupts the endosomal membrane at the pH range inside the endosomes in combination with (2) a second component which further enhances disruption and/or delivery of a therapeutic or diagnostic agent. The second component is conjugated or incorporated into the first polymer, and the composition optionally can be provided in a carrier such as nanoparticles, microparticles, and liposomes.

**II. Rejections Under 35 U.S.C. § 112**

Claims 1-20 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The

rejection is respectfully traversed if applied to the claims as amended.

The cancellation or amendment of claims 1, 3, 7, and 11-13 is believed to moot the rejections and/or specific queries posed in the Office Action with respect to these claims.

With respect to the Examiner's question about claim 19, see for example page 25, lines 6-12 and the Examples. One skilled in the art understands that if a lipid membrane, for example covering a cell, is disrupted, then materials can pass both into and out of the cell. The claims as amended are clear and definite to one skilled in the art when read in light of applicants' specification.

**III. Rejections Under 35 U.S.C. § 102**

Claims 1-3, 5-6, 8-10, 13, 15, and 17-19 were rejected under 35 U.S.C. § 102(a) as anticipated by PCT WO 98/33520 by Bystryn ("Bystryn"). Claims 1-3, 5-7, 9-15, 18, and 19 were rejected under 35 U.S.C. § 102(a) as anticipated by U.S. Patent No. 5,609,590 to Herbig et al. ("Herbig"). Claims 1-16 and 18-20 were rejected under 35 U.S.C. § 102(a) as anticipated by PCT WO 97/04832 by Mitragotri, et al. ("Mitragotri") or PCT WO 97/09068 by Hoffman and Stayton ("Hoffman"). Claims 1-7, 9, 10, 14-16, and 18-20 were rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,807,306 to Shapland et al. ("Shapland"). Claims 1-3, 5-6, 8-13, 15, and 17-19 were rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,753,263 to Lishko et al. ("Lishko"). Claims 1-7, 9, 15, and 18-20 were rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 5,362,308 to Chien ("Chien"). The rejections are respectfully traversed if applied to the amended claims.

Bystryn

Bystryn is not prior art under 35 U.S.C. § 102(a), because it was published 6 August 1998, and the present application claims priority to U.S. provisional application 60/070,441, filed January 5, 1998, which is more than seven months prior to Bystryn's publication. It is not apparent from the Office Action what "issue" the Examiner requests clarification with respect to Bystryn.

Nonetheless, Bystryn discloses a vaccine composition which includes an antigen and an immunomodulator delivered in a carrier, such as a pH sensitive liposome prepared from dioleoylphosphatidylethanolamine and cholesteryl hemisuccinate. There is no disclosure or suggestion in Bystryn of a pH-sensitive *polymer* conjugated to or having incorporated therein a second polymeric or monomeric unit which enhances disruption of the membrane or bonds to a carrier or a therapeutic or diagnostic agent.

Herbig

Herbig discloses osmotic bursting devices for dispensing a drug in an aqueous environment (abstract). The devices utilize a pH sensitive material coating a drug capsule, such that the pH sensitive material is semipermeable to water and causes hydrostatic pressure within the capsule to build and eventually burst the capsule, or the pH sensitive material is used to hold together two capsule portions until it degrades in contact with an environment having a particular pH to release the capsule contents (col. 6, lines 40-58). There is no disclosure or suggestion in Herbig, however, of a pH-sensitive polymer which is membrane disruptive at a pH between about 5 and 6.5 and which is conjugated to or has incorporated therein a second polymeric or

monomeric unit which enhances disruption of the membrane or bonds to a carrier or a therapeutic or diagnostic agent.

Mitragotri

Mitragotri discloses the transdermal transport of drugs using low frequency ultrasound, chemical modifiers of permeability and/or cavitation, iontophoresis and/or electroporation, pressure and/or vacuum and magnetic force fields (abstract). Mitragotri discloses that delivery is enhanced using liposome or microparticle drug carriers, particularly with microparticles having surfaces with increased hydrophilicity or lipophilicity (abstract). There is no disclosure or suggestion in Mitragotri, however, of a pH-sensitive polymer which is membrane disruptive at a pH between about 5 and 6.5 and which is conjugated to or has incorporated therein a second polymeric or monomeric unit which enhances disruption of the membrane or bonds to a carrier or a therapeutic or diagnostic agent.

Hoffman

Hoffman discloses stimuli-responsive polymers conjugated to interactive molecules. The function of the interactive molecule is controlled by a change in an external stimuli, such as temperature or pH, and the change cause the polymer to undergo a conformational or physico-chemical change which leads to a structural transition at or near or distant to the site of attachment, thereby modulating the activity of the interactive molecule in the process (p. 9, lines 9-23). There is no disclosure or suggestion in Hoffman, however, of a pH-sensitive polymer which is membrane disruptive at a pH between about 5 and 6.5 *and which is conjugated to or has incorporated therein a second polymeric or monomeric unit which enhances disruption of*

*the membrane or bonds to a carrier or a therapeutic or diagnostic agent.*

Shapland

Shapland discloses a drug delivery apparatus and method for delivering a drug encapsulated in a polymeric matrix to internal body tissue using a catheter device and iontophoresis or phonophoresis (abstract). Shapland fails, however, to disclose or suggest a pH-sensitive polymer which is membrane disruptive at a pH between about 5 and 6.5 and which is conjugated to or has incorporated therein a second polymeric or monomeric unit which enhances disruption of the membrane or bonds to a carrier or a therapeutic or diagnostic agent.

Lishko

Lishko discloses encapsulation of compounds in liposomes for targeted delivery to hair follicles (col. 3, lines 19-38). Lishko fails, however, to disclose or suggest a pH-sensitive polymer which is membrane disruptive at a pH between about 5 and 6.5 and which is conjugated to or has incorporated therein a second polymeric or monomeric unit which enhances disruption of the membrane or bonds to a carrier or a therapeutic or diagnostic agent.

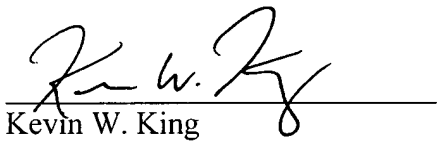
Chien

Chien discloses disposable dosage units for use in iontophoresis-facilitated transdermal delivery (abstract). The dosage unit includes a first hydrophilic gel polymer layer in which an ionic exchange resin is dispersed; a permselective layer; a second hydrophilic gel polymer layer in which a ionized pharmaceutical solution is dispersed; a thin fabric disk; and an adhesive polymer layer (col. 2, lines 18-45). There is no disclosure or suggestion in Chien, however, of a pH-sensitive polymer which is membrane disruptive at a pH between about 5 and 6.5 and which

is conjugated to or has incorporated therein a second polymeric or monomeric unit which enhances disruption of the membrane or bonds to a carrier or a therapeutic or diagnostic agent.

Applicants therefore respectfully request allowance of claims 1, 5, 7-13, 15, and 17-32.

Respectfully submitted,



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